REMARKS

The indicated allowability of claims 2 and 4-12 is noted with appreciation. The above amendments to claims 13 and 15, and the below remarks and the accompanying declaration of Susan Elizabeth Ashton (hereinafter "the Ashton Declaration"), are believed to now place all claims in condition for allowance.

Claim Amendments

Claim 13 has been amended to clarify the grammar of subparagraph (d) of claim 13 in the manner suggested by the Examiner. Claim 15 has been amended to remove the superfluous recitation "such as a human being," and to change "in need of such treatment" to more appropriately read "in need thereof," since there is no antecedent basis for the term "treatment.".

Following entry of these amendments, claims 2 and 4-15 remain pending in this application.

Claim Rejection – 35 USC §112, First Paragraph

Claims 14 and 15 have been rejected under 35 U.S.C. §112, first paragraph, as not being enabled by the specification. The Examiner asserts that enablement "is lacking for therapeutic methods," and suggests at page 5 of the Action that the term "pharmaceutical" be deleted from composition claim 14. The Examiner further suggests that the term "treatment" be removed from claim 15, and that the claim be directed toward a method of "reducing the vascular volume of blood vessels" as opposed to the present "method for producing a vascular damaging effect."

Any basis for these grounds for rejection is believed to be overcome by the above amendments and the accompanying evidence, but to the extent not overcome, these grounds for rejection are respectfully traversed.

As pointed out on pages 1 and 2 of the specification, normal angiogenesis plays an important role in a variety of processes, but the formation of new vasculature by angiogenesis, or neovascularization, is a key pathological feature of several diseases. For

example, for a solid tumor to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients. The present application is based on the discovery of novel compounds that can reverse neovascularation by damaging the newly-formed vascular endothelium. Thus, it is believed that the use of compounds of the invention damages newly-formed vasculature, such as the vasculature of tumors, thus effectively reversing the process of angiogenesis as compared to known anti-angiogenic agents, which function by impeding the development of new vasculature and tend to be less effective once the vasculature has formed.

The Examiner suggests that claim 15 be redirected toward a method of reducing the vascular volume of blood vessels in a warm-blooded animal in need thereof by administering an effective amount of a compound according to claim 2. While the Examiner's suggestion is appreciated and supported by the specification, Applicants would prefer to keep claim 15 directed toward the action of the claimed compounds, *i.e.*, producing a vascular damaging effect. This effect is demonstrated with respect to representative compounds of the Examples by the data submitted with the accompanying Ashton Declaration, which is believed to fully enable claim 15 as amended above.

Thus, as noted in paragraph 7 of the Ashton Declaration, the table of Appendix I reports data from assays (discussed in paragraph 5 of the Declaration and at pages 52 and 53 of the specification) for representative exemplified compounds. These data show the activity of the tested compounds as vascular damaging agents, including data from the human umbilical vein endothelial cell (HUVEC) detachment assay and the Hras5 necrosis model. As noted in the Declaration, certain of these compounds are identified as "prodrugs" in the sense that the exemplified compound is converted to the active moiety *in vivo*, after administration to a the warm blooded animal. Thus, for these compounds, only data for the *in vivo* Hras5 model is included since it would be expected that these "prodrugs" would only have low activity in the *in vitro* HUVEC detachment assay. The declaration further reports that, when establishing the Hras5 necrosis model, no adverse events were observed either when dosing representative compounds to non-tumor bearing male nude mice or when dosing Appendix I examples to tumor bearing male nude mice during the 24 hour period of the assay.

The declaration concludes in paragraph 8, that these data "demonstrate that the tested compounds inhibit tumour growth in an *in vivo* tumour model, and produce a vascular damaging effect as shown by an effect *in vitro* on endothelial cells in the HUVEC detachment assay, which is translated to an anti-tumour effect *in vivo* in the Hras necrosis model."

It is therefore respectfully submitted that any basis for the rejection of claims 14 and 15 on the assertion that the specification is not enabling for "therapeutic methods" or the production of a vascular damaging effect has been overcome.

Claim Rejection - 35 USC §112, Second Paragraph

Claims 13 and 15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

This rejection of claim 13 has been overcome by the above amendment to claim 13, clarifying the objected-to phrase of subparagraph (d) to read, "the reaction of a compound of formula III or IV by glycosylation reactions. An example of a glycosylation reaction can be found in the specification on page 46, lines 25-31. In addition, glycosylation reactions are well known in the art, and thus the skilled person would be familiar with the term glycosylation and understand the types of chemical reactions this would cover. This is demonstrated, for example, by two literature publications illustrating glycosylation of another small molecule vascular damaging agent, combretastatin A-4:

Orsini at al (1997) Carbohydrate Research 301, 95-109; and

Brown e1 al (1995) J.Chem.Soc.Perkin. Trans. 1 577-581

These references are attached hereto, and are formally cited in the accompanying form PTO-1449.

Claim 15 has been rejected as being indefinite with respect to the nature of the "vascular damaging effect." This ground for rejection is respectfully traversed. To the extent a person skilled in the art was not already familiar with the concept of "vascular damaging effect," the specification clearly describes the intended meaning of the term "vascular damaging effect" as used in the claims. In this regard, the Examiner is referred to page 1, lines 24-25, where it teaches that the compounds of the invention specifically

damage newly formed vasculature, and to page 1, lines 16-18, where the specification describes the requirement of the tumor to develop its own blood supply and the consequences to the tumor of damaging this blood supply. The phrase "vascular damaging effect" would be understood by persons skilled in the art, and therefore is not indefinite. It is respectfully requested that this ground for rejection be withdrawn.

Information Disclosure Statement

The Examiner has noted that a number of documents cited in the form PTO-1449 submitted September 8, 2004 were "not received," and therefore were not considered. A full set of the cited documents was, in fact, submitted with the Information Disclosure Statement filed on September 8, 2004, stapled together in groups, which groups were in turn stapled to one another so that they would not get misplaced during processing, as so often happens with Information Disclosure Statements of this size. Nevertheless, it can only be assumed that some of the documents were misplaced in processing before the file reached the Examiner. Therefore, a further form PTO-1449 is being submitted with this Amendment and Response, citing and submitting a further copy of each of the documents that was crossed out as not being considered by the Examiner on the September 8, 2003 form PTO-1449. Additionally, translations of the Russian language Kiselev et al. references have been submitted, and note on the PTO-1449. It is respectfully requested that each of these documents be considered by the Examiner, and such consideration acknowledged by returning an initialed copy of the PTO-1449 to the undersigned.

Conclusion

In view of the above amendments, the evidence submitted with the Ashton Declaration, and the above remarks, it is believed that all grounds for rejection have been addressed and overcome. Therefore, withdrawal of the rejection of claims 13-15 is believed to be in order, and the allowance of these claims together with already-allowed claims 2 and 4-12 is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required,

including any required extension of time fees, or to credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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